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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/783,580	02/15/2001	Lawrence E. Cornett	023533-0113	4347

22428 7590 06/25/2004

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 06/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/783,580	CORNETT ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 April 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,8-13,15-31,33-35,38 and 44-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-5,8-13,15-31,33-35,38 and 44-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

Claims 1-5, 8-13, 15-31, 33-35, 38, and 44-57 remain rejected under 35 U.S.C. 112, first paragraph, for the reasons of record set forth in the Office action of 6/7/02, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The third Cornett declaration under 37 CFR 1.132 filed 4/22/04 is insufficient to overcome the rejection of claims 1-5, 8-13, 15-31, 33-35, 38, and 44-57 for lack of an enabling disclosure as set forth in the last Office action.

Declaration ¶ 3-8 expand discussion of the evidence described in ¶ 3 of the 10/16/03 declaration. It is not questioned that this evidence shows delivery and expression of a gene encoding β_2AR to the lungs of normal rats, or even that the expression resulted in a modest effect on airway resistance. The declaration indicates that the modest effect was observed when the AAV were delivered by nebulization but not by bolus administration. However the declaration does not indicate whether the consistent, modest reduction in Newtonian resistance observed for the treated rats was statistically significant. In ¶ 7, declarant cites Gomes et al. as showing that rodent lung was a valid general-purpose model of the human lung. However, this reference does

not suggest that the normal rodent lung is a valid model of the lung of a human with an airway disease, such as asthma. The issue is not whether every airway epithelial cell would need be transfected, but what proportion of them need be transfected and whether such a proportion could be transfected with the vectors described in the specification and by the methods described in the specification. The declaration fails to provide evidence that the results of this experiment are predictive of treatment of asthma or any other airway disease.

Declaration ¶ 9 describes an experiment were the AAV expressing β_2AR were tested in allergen-sensitized Brown-Norway rats. It is not clear from the description of the experiment in what order and timing some of the steps were performed, specifically initial sensitization with ovalbumin and treatment with AAV. The results appear to show a modest resistance to methacholin-induced airway resistance in AAV treated rats, which Declarant attributes to expression of β_2AR. Elwood et al. is cited in ¶ 10 to indicate that the allergen-sensitized Brown-Norway rat model system is used in the art to study asthmatic lung. However, Elwood clearly indicates that this model is used to elucidate the role of eosinophils and lymphocytes in the pathogenesis of human allergic airway inflammatory responses. Elwood does not suggest that this model system is useful for testing potential treatments of asthma or any other airway disease. Factor (2003) discusses this type of model system in the last paragraph (page 151). It notes that while current paradigms of asthma are based on such models, that asthma is likely to be a phenotype of an as yet undefined polygenic mechanism, and concludes that "the absence of a central pathophysiological process responsible for increases in airway resistance an inflammation make asthma a yet formidable target for gene therapy." In other words, while the allergen-induced airway models are useful for study of asthma, they are not models of asthma. The

declaration fails to provide evidence that the results of this experiment are predictive of treatment of asthma or any other airway disease. With respect to McGraw et al. (¶ 11), at best this reference supports the conclusion that resistance to methacholin-induced airway resistance in AAV treated rats was due to expression of β_2AR, and the hypothesis that delivery of a β_2AR gene to lung epithelia might be a useful treatment for airway constriction. The reference does not suggest how such treatment would be accomplished however.

In ¶ 12, Declarant attempts to dismiss the "known issues" responsible for the high unpredictability and general lack of success in gene therapy, as discussed in Factor (2001), Orkin and Demoly. The fact that the claimed method is augmentation therapy, i.e. to augment endogenous expression of a desired gene product, is not relevant to most of the issues raised in Orkin, such as ineffective vectors, inadequate understanding of the pathophysiology of the target disease, inefficient delivery of vectors to the appropriate target cells, poor predictability of animal models. Both Factor and Demoly discuss "augmentation" therapies, and Factor discusses the therapy being claimed. Furthermore, Factor (2003), published well after the instant application was filed, also describes the therapy being claimed among other potential gene therapies for asthma, and indicates (page 151, col. 1-2) "numerous hurdles remain before therapeutic gene transfer for asthma can be considered," that the first hurdle is affecting efficient gene transfer to the airway epithelium and the ability of adenovirus and AAV to transfect airway epithelium is limited, and other hurdles include overcoming the normal physical and immunological barriers to gene deliver, as well as the "significant obstacle" posed by the asthmatic lung due to inflammation-induced loss of epithelial cells and increased mucous and edema.

Whether the delivery of β_2AR through gene therapy can be developed in to an effective treatment for asthma, or any other airway disease, remains to be seen. First, the substantial known impediments to such treatment must be overcome to even determine if such delivery would be a useful treatment, and the instant specification does not address these impediments, much less teach how to overcome them.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (571) 272-0733. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Amy J. Nelson can be reached on (571) 272-0804. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Scott D. Priebe

Scott D. Priebe
Primary Examiner
Art Unit 1632